Nucleophilic Aromatic Substitution on 4-Fluorophenylsulfonamides: Nitrogen, Oxygen, and Sulfur Nucleophiles

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Abstract: Improved conditions are reported for the stoichiometric reaction of nitrogen, oxygen, and sulfur nucleophiles with weakly activated 4-fluorophenylsulfonamides.

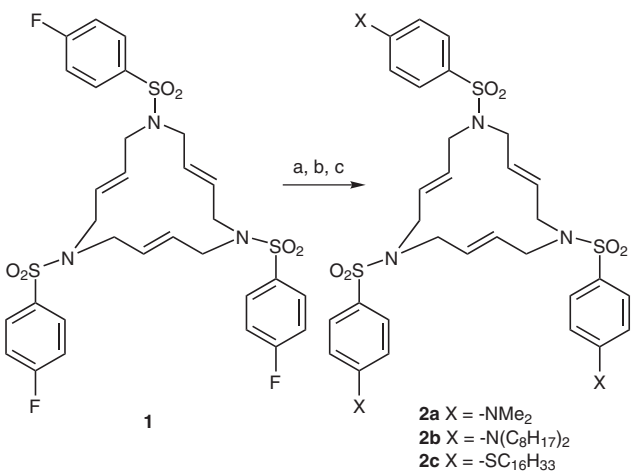
Key words: nucleophilic aromatic substitution, phase transfer catalysis, cesium, macrocycles, diaryl oxides, diarylamines

In the course of a project we sought substitution of fluorine with nucleophiles in triolefinic macrocycle **1** (Scheme 1)[1,2] Large excesses of nucleophiles and harsh experimental conditions were required. This solution is not applicable to reactions of more valuable nucleophiles when only one mol of nucleophile per fluorine atom is preferred. Milder experimental conditions are also desirable.

Whereas nucleophilic aromatic substitution (S_NAr) on 4-nitrofluoroaromatics is a reaction of broad applicability,[4] activation by electron-acceptor functional groups other than nitro has met with less success. This is a consequence of the decreased ability to stabilize the negative charge in the intermediate anion formed along S_NAr processes. The stabilizing power can be estimated from the σ_p^- values of the different groups: -NO_2 (1.27), -SO_2-CH_3 (1.13), and -SO_2-NMe_2 (0.99).[5] Therefore it is not surprising that reports on replacement of fluorine on aromatic sulfones with nitrogen,[6] oxygen,[7] or sulfur[8] nucleophiles are scarce. In these cases either large excess of nucleophiles, or severe experimental conditions, or both had to be introduced. Examples of such a reaction on 4-fluorophenylsulfonamides are even more rare.[1,9]

We endeavored to find improved methods to perform S_NAr reactions on aromatic fluorosulfonamides choosing sulfonamide **3** as a model.[10]

We report here that fluorine can be exchanged in compound **3** with a variety of primary and secondary aliphatic and aromatic amines (Table 1) through their lithium amides formed with buthyllithium in THF (method A).[11,12] Thus, hexylamine, di-*n*-octylamine, and diethylamine react to afford **4a**,**b**,**d** in good yields (entries 1, 2, and 5). However, laurylamine did not react under conditions of method A. Nevertheless, reaction did occur in hot DMF in the presence of potassium carbonate (method B) to afford **4c** (entries 3 and 4). Aniline and a N-substituted aniline, 4-chloro-*N*-methylaniline, were also active under method A (entries 6 and 7), diarylamines **4e**,**f** being isolated in reasonable yields. Finally, 1-aza-18-crown-6 gave **4g** (entry 8). Stoichiometric amounts or only slight excesses (1.2 molar) of amine were used in all cases. Cyclohexylamine and diphenylamine were inert under all tested conditions. Addition of tetramethylethylenediamine (TMEDA) did not improve the results. Even in one case, when working with di-*n*-octylamine, a small amount of **4** ($R^1 = R^2 = CH_3$) was isolated. Dimethylamine required for the formation of this by-product must come from TMEDA under BuLi initiation as suggested by one referee. Therefore this additive was not considered further.



Scheme 1 a) Excess 2 M $HNMe_2$ in THF, 100 °C, 6 d in closed reactor; b) excess $HN(C_8H_{17})_2$, THF, 170 °C, 2 months in closed reactor; c) $HSC_{16}H_{33}$ (3-fold molar excess), K_2CO_3, DMSO, 100 °C, 2 d.[3]

Oxygen nucleophiles react with **3** (Scheme 2 and Table 2) to afford the corresponding ethers. Thus, three aliphatic alcohols as well as phenol gave ethers **5a**–**d** in good yields when their sodium salts (HNa in THF) were treated with **3** (entries 1, 3–5, Table 2). We noticed that addition of tetrabutylammonium chloride (method C) improved the result. In theory the ammonium salt could be used in substoichiometric amounts since it is a catalyst. Indeed, formation of sodium chloride generates the quaternary salts $Bu_4N(RX)$ which, upon reaction, regenerate the quaternary salt in the form of fluoride. We never made attempts to

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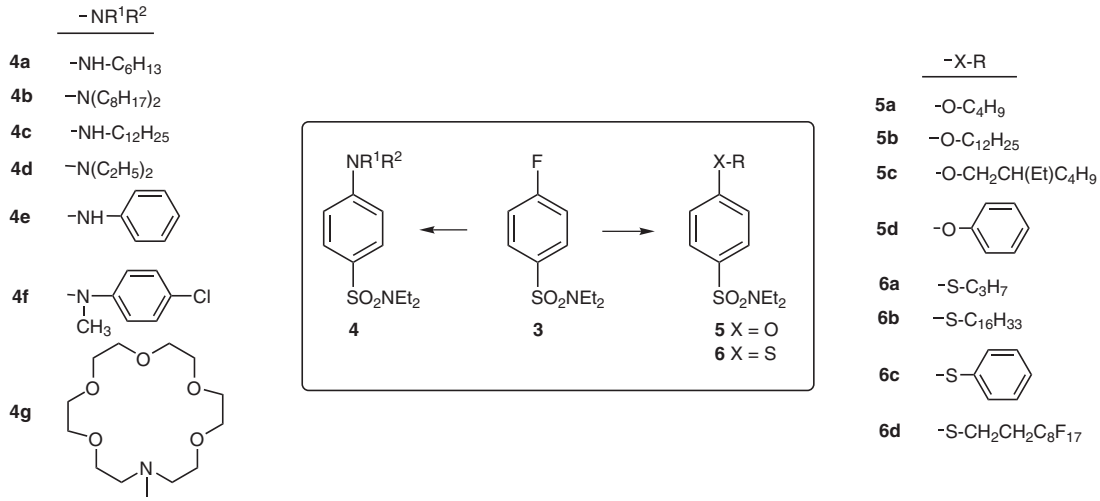

Scheme 2 Replacement of fluorine by amines (Table 1), alcohols, and thiols (Table 2).

use Bu_4NF as catalyst. Since the ammonium was easily eliminated in the working up we decided to use one mol of Bu_4NCl for oxygen nucleophiles.[13]

Cesium carbonate is an interesting alternative. Thus, lauryl ether **5b** was obtained by treating the alcohol with **3** in THF in the presence of Cs_2CO_3 and Bu_4NCl (method D, entry 2, Table 2).[14] All attempts to make ethers from fluorinated 1*H*,1*H*,2*H*,2*H*-perfluorodecanol or 1*H*,1*H*,2*H*,2*H*-perfluorooctanol failed, both by methods C or D.

Finally sulfur nucleophiles were tested under conditions C and D (Scheme 2 and Table 2). Thus, excellent results were secured for both aliphatic and aromatic thiols that gave sulfides **6a–c** in excellent yields (entries 6–8, Table 2) in the presence of substoichiometric amounts of Bu_4NCl. Cesium carbonate, always in the presence of Bu_4NCl, also was used successfully (entry 9). The heavily fluorinated 1*H*,1*H*,2*H*,2*H*-perfluorodecanethiol gave no complete reaction under method C (entry 10). However, the use of cesium carbonate (method D) gave excellent results (entries 11, 12).

In summary we present in this letter methods to perform S_NAr reactions of weakly activated 4-fluorophenylsulfonamides. Furthermore, we tested our method on macrocycle **1** (Scheme 3). Thus, a triple substitution was achieved by reaction of **1** with 1*H*,1*H*,2*H*,2*H*-perfluorodecanethiol under method D conditions using 1.4 mol of thiol per fluorine atom to afford macrocycle **7** (mp 187–192 °C) in 95% yield.

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Financial support from Ministerio de Ciencia y Tecnología (Project BQU 2002-04002) and Generalitat de Catalunya (Project 2001SGR00181 and 'Distinció per a la Promoció de la Recerca Universitaria' (to M.M.-M) is gratefully acknowledged. R.M.S. was incorporated into the research group through a 'Ramón y Cajal' contract (MCyT-FEDER/FSE). We thank one referee for a helpful suggestion on the formation of dimethylamine.

Table 1 Replacement of Fluorine in Sulfonamide **3** with Amines[a]

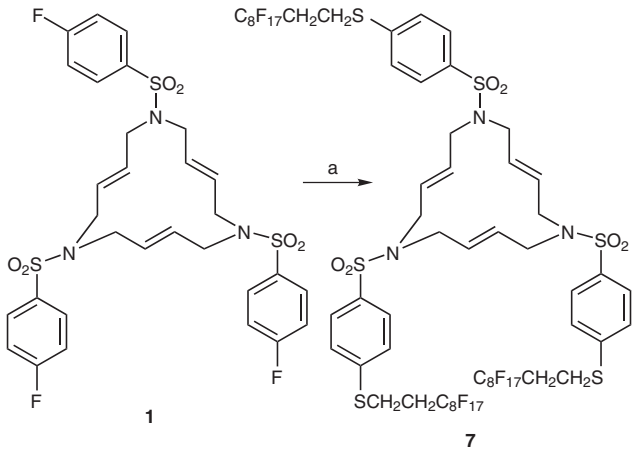
Entry	Yield of **4** (%)	R^1	R^2	Mp (°C)	Method
1	**4a** (74)	H	C_6H_{13}	Oil	A
2	**4b** (100)	C_8H_{17}	C_8H_{17}	Oil	A
3	**4c** (80)	H	$C_{12}H_{25}$	45	B
4	**4c** (0)	H	$C_{12}H_{25}$		A
5	**4d** (93)	C_2H_5	C_2H_5	35–39[b]	A
6	**4e** (53)	H	C_6H_5	71–74	A
7	**4f** (62)	CH_3	C_6H_4-Cl-4	142–144	A
8	**4g** (59)	-$(CH_2CH_2O)_5CH_2CH_2$-		Oil	A

[a] Method A: BuLi, THF. Method B: K_2CO_3, DMF, 160 °C (bath temperature).
[b] Picrate: mp 109–110 °C.

Table 2 Replacement of Fluorine in Sulfonamides **1** and **3** with Oxygen and Sulfur Nucleophiles[a]

Entry	Yield of **5**–**7** (%)	X-R	Bu_4NCl (mol)	Mp (°C)	Method
1	**5a** (61)	O-C_4H_9	1	60–62	C
2	**5b** (83)	O-$C_{12}H_{25}$	1	33–35	D
3	**5b** (80)[b]	O-$C_{12}H_{25}$	1	–[b]	C
4	**5c** (76)	O-$CH_2CH(Et)$-C_4H_9	1	Oil	C
5	**5d** (83)	O-Ph	1	80–82	C
6	**6a** (87)	S-C_3H_7	0.01	59–61	C
7	**6b** (81)	S-$C_{16}H_{33}$	0.06	41–43	C
8	**6c** (73)	S-Ph	1	63–66	C
9	**6c** (61)	S-Ph	1	63–66	D
10	**6d** (80)[b]	S-CH_2CH_2-C_8F_{17}	1	56–58	C
11	**6d** (84)	S-CH_2CH_2-C_8F_{17}	0.01	56–58	D
12	**7** (95)	S-CH_2CH_2-C_8F_{17}	0.1	187–192	D

[a] Method C: NaH. Method D: Cs_2CO_3. In both methods: Bu_4NCl, THF.
[b] Conversion. Product not isolated.



Scheme 3 Triple substitution. a) $HSCH_2CH_2C_8F_{17}$ (4.2 mol); conditions D.

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(3) Compound **2a** (72%): mp 230 °C. Compound **2b** (40%): oil. Compound **2c** (65%): mp 84–85 °C.

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(10) Compound **3**, mp 39–40 °C, was prepared by reaction of 4-fluorobenzenesulfonyl chloride with diethylamine in CH_2Cl_2.

(11) **Method A of Table 1. Typical Experiment:**
A 1.6 M solution of *n*-BuLi in hexane (3.4 mL, 5.34 mmol) was added dropwise into a solution of di-*n*-octyl amine (1.1 mL, 3.56 mmol) in anhyd THF (3 mL) cooled at –40 °C (MeCN–liquid nitrogen bath). The mixture was stirred at –40 °C for 15 min. Then, a solution of sulphonamide **3** (0.82 g, 3.56 mmol) in anhyd THF (5 mL) was added. The mixture was stirred at r.t. for one day and evaporated. The residue was partitioned between $CHCl_3$ and diluted HCl, the organic layer was dried (Na_2SO_4) and evaporated to afford 1.6 g (ca. 100%) of **4b** as an ochre oil. IR (Attenuated Total Reflectance, ATR): 2924, 2853, 1594, 1333, 1147 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.6 Hz, 6 H), 1.12 (t, *J* = 7.2 Hz, 6 H), 1.29 (m, 20 H), 1.57 (m, 4 H), 3.18 (q, *J* = 7.2 Hz, 4 H), 3.26 (t, *J* = 7.1, 4 H), 6.56 (d, *J* = 9.1 Hz, 2 H), 7.57 (d, *J* = 9.1 Hz, 2 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.2, 14.4, 22.7, 27.2, 29.4, 29.5, 31.9, 42.1, 51.1, 110.5, 124.7, 129.1, 150.8. Anal. Calcd for $C_{26}H_{48}N_2O_2S$: C, 68.98; H, 10.69; N, 6.19; S, 7.08. Found: C, 68.79; H, 10.69; N 6.05; S, 6.74.
Good elemental analyses (at least three elements) were secured for **4b**,**c**,**e**–**g** (with 0.5 mol of H_2O), and **4d** (as picrate, mp 109–110 °C). Product **4a**: HRMS: *m*/*z* calcd for $C_{16}H_{28}N_2O_2S$: 312.1871; found: 312.1867.

(12) When our work was finished a paper was published on similar results obtained with 2-fluoropyridine: Pasumansky, L.; Hernández, A. R.; Gamsey, S.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **2004**, *45*, 6417.

(13) **Method C of Table 2; Typical Experiment**
A solution of **3** (1.05 g, 4.55 mmol) and tetrabutylammonium chloride (1.52 g, 5.2 mmol) in anhyd THF (5.5 mL) was added under argon via cannula to a stirred suspension of sodium phenolate in anhyd THF (4 mL), made from NaH (60% suspension in mineral oil, 0.30 g, 7.55 mmol) and phenol (0.52 g, 5.52 mmol). The mixture was stirred overnight and MeOH (2 mL) was added. The solvents were evaporated and the residue was taken in EtOAc. The organic solution was washed with 5% aq NaOH, dried (Na_2SO_4), and evaporated to afford a dark yellow oil that crystallized upon standing (83%). It was recrystallized from *t*-butyl methyl ether to afford pure **5d** (52%); mp 80–82 °C. IR (ATR): 3090, 2972, 2932, 2879, 1579, 1491, 1332, 1238, 1200, 1169, 1089, 1014, 934 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.0 Hz, 3 H), 3.23 (q, *J* = 7.0 Hz, 4 H), 7.02 (d, *J* = 9.0 Hz, 2 H), 6.94–7.08 (m, 2 H), 7.21 (tt, *J* = 6.9 and 1.2 Hz, 1 H), 7.40 (m, 2 H), 7.75 (d, *J* = 9.0 Hz, 2 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 14.2, 42.0, 117.6, 120.2, 124.8, 129.1, 130.1, 134.2, 155.3, 161.1. HRMS calcd for $C_{16}H_{19}NO_3S$: 305.1086; found: 305.1100.
Good elemental analyses (at least three elements) were secured for **5a**–**c**, **6a**–**d**, and **7**.

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